A13 cont. subdomain comprising an amino acid sequence from a third, different member of said superfamily.

REMARKS

Applicants thank the Examiner and his supervisor, Gary Kunz, for the helpful comments and suggestions during the telephonic interview on November 16, 2001.

In response to the Examiner's rejections and in order to expedite prosecution, applicants have canceled claims 4 and 8-17 without prejudice and without waiver of their right to file for and obtain claims directed to any non-elected subject matter in divisional and continuing applications which claim priority from this application.

Applicants note that the Examiner has withdrawn claims 4 and 7 from further consideration. However, claims 4 and 7 are encompassed by elected Group I. Applicants have canceled claim 4 in response to this Office Action. Accordingly, applicants request that the Examiner not withdraw claim 7 from further consideration.

Applicants have amended claims 1, 3, 5 and 7 to improve their form and to incorporate the Examiner's and the Examiner's supervisor's comments as discussed during the telephonic interview on November 16, 2001.

Applicants have amended claim 1 to recite that the finger 2 subdomain is CDMP-2 (residues 68-98 of SEQ ID NO:86) and that the finger 1 or heel subdomain, comprise at least a portion of amino acid sequence from at least a second, different member of the TGF-β superfamily.

Applicants have amended claim 3 to recite a chimeric protein according to claim 1 wherein the second TGF-β superfamily member is selected from the group consisting of TGF-β1 (SEQ ID NO: 40), TGF-β2 (SEQ ID NO: 41), TGF-β3 (SEQ ID NO: 42), TGF-β4 (SEQ ID NO: 43), TGF-β5

(SEQ ID NO: 44), dpp (SEQ ID NO: 45), Vg-1 (SEQ ID NO: 46), Vgr-1 (SEQ ID NO: 47), 60A (SEQ ID NO: 48), BMP-2A (SEQ ID NO: 49), BMP-3 (SEQ ID NO: 50), BMP4 (SEQ ID NO: 51), BMP5 (SEQ ID NO: 52), BMP-6 (SEQ ID NO: 53), Dorsalin (SEQ ID NO: 54), OP-1 (SEQ ID NO: 55), OP-2 (SEQ ID NO: 56), OP-3 (SEQ ID NO: 57), GDF-1 (SEQ ID NO: 58), GDF-3 (SEQ ID NO: 59), GDF-9 (SEQ ID NO: 60), Inhibin α (SEQ ID NO: 61), Inhibin βA (SEQ ID NO: 62), Inhibin βB (SEQ ID NO: 63), CDMP-1/GDF-5 (SEQ ID NO: 83) and GDF-7 (SEQ ID NO: 87). Support for this amendment is provided throughout the specification (see, e.g., pages 27-29 of the specification).

Applicants have amended claims 5 and 7 to improve their form.

None of these amendments adds new matter.

Applicants now address the Examiners objections and rejections.

THE RESTRICTION REQUIREMENT

The Examiner has withdrawn claims 4 and 7-17 from further consideration and has recast the restriction requirement as follows:

Group I: Claims 1-7, drawn to a protein comprising a dimer wherein the monomers are chimeras of TGF-β superfamily members;

Group II: Claims 8-14, to the extent that they are drawn to a recombinant method of protein synthesis;

Group III: Claims 9-14, to the extent that they are drawn to an enzymatic method of protein synthesis;

Group IV: Claims 9-14, to the extent that they are drawn to a non-recombinant method of protein synthesis;

Group V: Claims 15-16 to the extent that they are drawn to a method of tissue regeneration; and

Group VI: Claim, drawn to an immunoassay.

The Examiner states that inventions II and I, III and I, and IV and I are related as process of making and product made. The Examiner further states that these inventions are distinct because invention I could be made with either II, III or IV.

The Examiner states that inventions I and V and I and VI are related as product and process of use and are distinct because invention I could be used *in vitro* for the structure function analysis of a TGF-β superfamily member or could be used in inventions VI or V, respectively.

The Examiner states that the pairwise combinations of II and each of III-VI, III and each of IV-VI, IV and each of V-VI and V and VI are distinct because each member of the pair performs different functions, using different starting materials and/or process steps.

The Examiner also states that Groups I-VI are generic to a plurality of disclosed patentably distinct inventions comprising a single invention represented by a single invention selected from the group consisting of

a. a finger 1 subdomain derived from a second, different, single member of the TGF-β superfamily; and

b. a finger 1 subdomain derived from a third, different single member of the TGF-β superfamily; and

a single invention selected from the group consisting of

c. a heel subdomain derived from a second, different, single member of the TGF-β superfamily; and

d. a heel subdomain derived from a third, different single member of the TGF-β superfamily,

in combination with,

e. a finger 2 subdomain derived from a first single member of the TGF-β superfamily;

f. a conserved C-terminal cysteine domain of a single member of the TGF-β superfamily.

The Examiner states that each of the above inventions is distinct and independent, wherein each can be manufactured independently of the other and used for independent and distinct purposes. The Examiner further contends that based on the 37 TGF-β superfamily members presented in figure 1, it follows that there are 37x37x37x37=1,874,161 independent and distinct inventions.

The Examiner also states that claim 10 is generic to a plurality of disclosed patentably distinct species comprising the species listed in claim 10.

The Examiner also states that claims 15 and 16 are generic to a plurality of disclosed patentably distinct species comprising the species listed in claim 16.

Finally, the Examiner contends that applicant has constructively elected the finger 1 domain of hOP-1, the heel domain of hOP-1 and the finger 2 domain of CDMP-2, the conserved C terminal cysteine domain of hOP-1 and the species amino acid residues 2-29 of SEQ ID NO:55, amino acid residues 68-98 of SEQ ID NO:86, amino acid residues 35-65 of SEQ ID NO:55 and the C-terminal cysteine domain of hOP-1 (SEQ ID NO:55) for prosecution on the merits.

Applicants traverse the restriction of Groups I-VI and their further restriction into over 1.8 million inventions each. As discussed during a conference call on November 16, 2001, between Examiner David Romeo, the Examiner's supervisor, Gary Kunz, and applicants attorneys, Karen Mangasarian and Jane Gunnison, applicants believe that the restriction is improperly drawn. During the telephone conference, the Examiner's supervisor, Gary Kunz, recommended that applicants amend the claims as discussed during the teleconference and request that the Examiner reinstate the original restriction/species election issued on December 12, 2000 and March 28, 2001.

Applicants respectfully traverse the Examiner's contention that Groups I-VI are generic to a plurality of patentably distinct inventions. According to the Examiner's current restriction, applicants are not entitled to a generic claim to their invention. Moreover, applicants wish to point out that the restriction as proposed by the Examiner would necessitate the filing of an excessive number of patent applications and imposes a significant expense on applicants. The expense would, in fact, be prohibitive to any applicant, regardless of whether that applicant is entitled to claim small entity status.

As discussed during the teleconference, applicants request that the Examiner reinstate the restriction/species election issued on December 12, 2000 and March 28, 2001. Applicants maintain their election of the Group I invention and species election wherein finger 1 is residues 2-29 of SEQ ID NO: 55 (hOP-1), the heel is residues 35-65 of SEQ ID NO:55 (hOP-1) and finger 2 is residues 68-98 of SEQ ID NO 86 (CDMP-2) and the C-terminal cysteine skeleton of OP-1. To the extent that the current restriction requirement is viewed as a species election, applicants further elect BMP-2 as the third member for finger 1 (residues 2-29 of SEQ ID NO: 49) and heel (residues 35-64 or SEQ ID NO: 49) subdomains. Applicants also request that the Examiner reinstate claim 7 (now withdrawn) as it falls within Group I.

Applicants have also amended claim 1 pursuant to the discussion during the teleconference to recite that the finger 2 subdomain is CDMP-2 (residues 68-98 of SEQ ID NO:86) and that the finger 1 or heel subdomains, comprise at least a portion of amino acid sequence from at least a second, different member of said superfamily.

In view of the discussion during the teleconference and of the prohibitive expense which could, in effect, deprive applicants of the opportunity to patent their invention, applicants request that the Examiner reconsider the burden associated with the proposed restriction and, combine the groups as discussed during the November 16, 2001 teleconference.

However, pursuant to 37 C.F.R. § 1.143, applicants provisionally elect the claims of Group I, i.e., claims 1-7, and the finger 1 domain of hOP-1 (second member) and BMP-2 (third member), the heel domain of hOP-1 (second member) and BMP-2 (third member) and the finger 2 domain of CDMP-2, and the C-terminal cysteine skeleton of hOP-1 for initial substantive examination. This election is expressly without waiver of applicants' right to continue to prosecute and to obtain claims to the non-elected subject matter in divisional or continuing applications claiming priority herefrom or from a related application under U.S.C. § 120.

FORMAL MATTERS

U.S. Patent Application Numbers

The Examiner has objected to the disclosure stating that there are blank spaces where U.S. patent application serial numbers are supposed to be and that appropriate corrections should be made.

Applicants have amended the specification at pages 2 and 9 to insert the appropriate patent and patent application numbers. Accordingly, the Examiner's objection has been obviated.

Sequence Listing and SEQ ID NOS

Applicants acknowledge that the sequence listing has been entered.

The Examiner has objected to the disclosure stating that the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. The Examiner states that sequences are disclosed in the figures without the appropriate sequence identifier.

Applicants have amended the brief description of the drawings to insert the appropriate SEQ ID NOS. Accordingly, applicants request that the Examiner withdraw this objection.

THE REJECTIONS

35 U.S.C. § 112, second paragraph

Claims 1-7

The Examiner has rejected claims 1-7 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The Examiner states that claims 1-7 are indefinite over the recitation of finger 1, finger 2, or heel subdomain because it is unclear if finger 1, finger 2 or heel is intended or if a portion thereof is intended.

Applicants have amended claim 1 (and accordingly, claim 2-7, dependent thereon) to recite that the finger 2 subdomain is CDMP-2 (residues 68-98 of SEQ ID NO:86) and that the finger 1 or heel subdomain comprise at least a portion of the amino acid sequence from at least a second, different member of said superfamily. Accordingly, applicant respectfully requests that the Examiner withdraw this rejection.

Claims 1 and 5

The Examiner has rejected claims 1 and 5 under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner states that the recitation of the term "derived from" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree of derivation.

Applicants have amended claim 1 to recite a "TGF-β superfamily chimeric protein said chimeric protein comprising a dimer wherein one monomer comprises an amino acid sequence from at least two different members of said superfamily wherein the monomer comprises a finger 1 subdomain, a finger 2 subdomain and a heel subdomain, said finger 2 subdomain being cDMP-2 (residues 68-98), said finger 1 or heel subdomain comprising at least a portion of the amino acid sequence from at least a second, different member of said superfamily". Applicant believes that this amendment overcomes the Examiner's rejection.

35 U.S.C. § 103(a): Claims 1-3, 5 and 6

The Examiner has rejected claims 1-3, 5 and 6 under 35 U.S.C. § 103 as being unpatentable over Keck et al., U.S. patent 6,040,431 ("Keck") in view of Griffith et al., Proc. Natl. Acad. Sci, 93, pp. 878-883 (1996) ("Griffith"), Luyten et al., WO96/14335 ("Luyten"), Qian et al., Proc. Natl. Acad. Sci, 89, pp. 6290-6294 (1992) ("Qian") and Daopin et al., Science, 257, pp. 369-373 (1992) ("Daopin"). The Examiner states that Keck teaches a finger 1 domain of OP-1 comprising amino acid residues 2-29 of SEQ ID NO: 55, a heel domain of OP-1 comprising amino acid residues 35-65 of SEQ ID NO; 55 and a conserved C-terminal 7 cysteine domain of SEQ ID NO:55. The Examiner further states that Keck does not teach a chimeric protein

comprising a dimer wherein one monomer comprises an OP-1 finger 1 domain, an OP-1 heel domain and a CDMP-2 finger 2 domain. The Examiner states that Griffith teaches that all of the TGF-β superfamily members in Figure 6 of Griffith share the OP-1/TGF-β2 structural motif. The Examiner states that Luyten teaches the amino acid sequence of CDMP-2 and that CDMP-2 has chondrogenic activity *in vivo* but substantially no osteogenic activity. The Examiner states that Qian teaches that the use of chimeric molecules is a practical approach to investigating structure/function relationships in closely related proteins. The Examiner finally states that Daopin teaches that TGF-β2 and BMP2 are structurally similar and suggests that the only stable form of TGF-β2 in solution is a dimer. The Examiner then concludes that it would have been obvious to one of skill in the art at the time of applicants' invention to make a morphon as taught by Keck and to modify that teaching to make a chimeric protein comprising a dimer wherein one monomer comprises an OP-1 finger 1 and heel and a CDMP-2 finger 2 domain with a reasonable expectation of success. The Examiner further argues that one of skill in the art would be motivated to make the modification because the use of chimeric molecules would be a practical approach to investigating structure/function relationships of OP-1 and CDMP-2 and that the only stable form in solution of such a chimeric molecule would reasonably be expected to be a dimer. Applicants traverse.

This rejection is built on nothing but hindsight and an "obvious to try" hypothesis -- a standard for obviousness that has been rejected. Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 725 (Fed.Cir. 1990) ("An 'obvious-to-try situation' exists when a general disclosure may pique the scientist's interest ..."). Nothing in Keck,

Luyten, Griffith, Qian or Daopin either alone or in combination, teaches chimeric TGF-β superfamily member proteins comprising a dimer wherein one monomer comprises a CDMP-2 finger 2 domain and a finger 1 and heel domain comprising at least a portion of the amino acid sequence from at least one other member of the superfamily.

Keck discloses single chain analogs of the TGF-β superfamily wherein the analog comprises a finger 1, heel and finger 2 linked to each other via a linker. All the proteins disclosed in Keck are single chains. Nothing in Keck teaches or suggests a dimeric chimeric TGF-β superfamily member protein wherein one monomer comprises a CDMP-2 finger 2 domain and a finger 1 and heel domain comprising at least a portion of the amino acid sequence from at least one other member of the superfamily.

Luyten merely discloses the sequence of CDMP-2. Luyten does not even identify the finger 1, heel and finger 2 regions of the protein. Luyten does not teach or suggest chimeric proteins wherein the finger 2 subdomain is CDMP-2 and the finger 1 and heel domains comprise at least a portion of the amino acid sequence of at least a second, different member of the TGF-β superfamily. Accordingly Nothing in Luyten teaches or suggests the chimeric proteins as claimed in the instant application.

Griffith discloses that the TGF-β superfamily members are structurally similar. Griffith does not teach or suggest the dimeric chimeras. Accordingly, nothing in Griffith teaches or suggests the chimeric proteins as claimed in the instant application.

Qian teaches chimeras of TGF-β1 and TGF-β2 comprising amino acids 1-39 of TGF-β2 (similar but not identical to finger 1 subdomain) linked to residues 40-82 of TGF-β1 (similar but not identical to heel subdomain) linked

to residues 83-122 of TGF-β2 (similar but not identical to finger 2 subdomain). At best, Qian teaches a chimeric protein wherein the finger 1 and finger 2 subdomains are from the same member of the superfamily. Qian does not teach chimeras wherein the finger 2 subdomain is from a TGF-β superfamily member different from that of the finger 1 and heel subdomains.

Daopin teaches that TGF-β2 and BMP-2 are structurally similar and that the only stable form of TGF-β2 in solution is a dimer. Daopin does not disclose dimeric chimeras of TGF-β superfamily members. Nothing in Daopin teaches or suggests the chimeric proteins as claimed in the present application.

Moreover, nothing in Keck, Luyten, Griffith, Qian and Daopin to teach or suggest combining them to produce the claimed chimeric TGF-β superfamily proteins. There was also no general knowledge in the art prior to this invention that making chimeric TGF-β superfamily proteins would have enhanced properties such as folding, stability or solubility. Thus, at the priority date of this application, there would have been no motivation to combine Keck, Luyten, Griffith, Qian and Daopin, because none of their teachings or the general knowledge available in the art provided such motivation. As such, amended claims 1-3 and 5-7 are not rendered obvious by the disclosure of Keck in combination with Luyten, Griffith, Qian and Daopin.

CONCLUSION

In view of the foregoing remarks, applicants respectfully request consideration and early allowance of the pending claims in this application.

Respectfully submitted,

James F. Haley, Jr. (Reg. No. 27,794)
Karen Mangasarian (Reg. No. 43,772)
Attorney for Applicants
c/o FISH & NEAVE
1251 Avenue of the Americas
New York, New York, 10020-1104
Tel: (212) 596-9000

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IN THE CLAIMS

1. (Amended) A TGF-β superfamily chimeric protein [derived from at least two different members of said superfamily], said chimeric protein comprising a dimer wherein one monomer comprises an amino acid sequence from at least two different members of said superfamily; wherein the [one] monomer comprises a finger 1 subdomain, a finger 2 subdomain and a heel subdomain, said finger 2 subdomain being [derived from] CDMP-2 (residues 1-35 of SEQ ID NO:10) [a first member of said superfamily], said finger 1 or heel subdomain [being derived] comprising at least a portion of the amino acid sequence from at least a second, different member of said superfamily, wherein said monomer further comprises a conserved C-terminal cysteine skeleton.

2. The chimeric protein of claim 1, wherein said second member is OP-1 (SEQ ID NO: 39).

3. (Amended) The chimeric protein of claim 1, wherein said [first member is CDMP-2 (SEQ ID NO: 10) and said] second member is [OP-1 (SEQ ID NO: 39)] selected from the group consisting of TGF-β1 (SEQ ID NO: 40), TGF-β2 (SEQ ID NO: 41), TGF-β3 (SEQ ID NO: 42), TGF-β4 (SEQ ID NO: 43), TGF-β5 (SEQ ID NO: 44), dpp (SEQ ID NO: 45), Vg-1 (SEQ ID NO: 46), Vgr-1 (SEQ ID NO: 47), 60A (SEQ ID NO: 48), BMP-2A (SEQ ID NO: 49), BMP-3 (SEQ ID NO: 50), BMP4 (SEQ ID NO: 51), BMP5 (SEQ ID NO: 52), BMP-6 (SEQ ID NO: 53), Dorsalin (SEQ ID NO: 54), OP-1 (SEQ ID NO: 55), OP-2 (SEQ ID NO: 56), OP-3 (SEQ ID NO: 57), GDF-1 (SEQ ID NO: 58), GDF-3 (SEQ ID NO: 59), GDF-9 (SEQ ID NO: 60), Inhibin α (SEQ ID NO: 61), Inhibin βA (SEQ ID NO: 62), Inhibin βB (SEQ ID NO: 63), CDMP-1/GDF-5 (SEQ ID NO: 83) and GDF-7 (SEQ ID NO: 87).

5. (Amended) The chimeric protein of claim 1, wherein said finger 1 subdomain is [derived] from OP-1 (SEQ ID NO: 55) [39), said finger 2 subdomain is derived from CDMP-2 (SEQ ID NO: 10)], and said heel domain comprises at least a portion of the heel domain of OP-1 (SEQ ID NO: [39)] 55).

7. (Amended) The chimeric protein of claim 1, wherein said monomer further comprises a finger 1 or heel subdomain [derived] comprising an amino acid sequence from a third, different member of said superfamily.

APPENDIX OF AMENDMENTS

IN THE SPECIFICATION

Page 2, the paragraph under the title "Continuing Application Data":

The instant utility application is based on provisional patent application 60/103,418 filed on October 7, 1998, the entire contents of which is herein incorporated by reference; and, the instant application is related to co-pending utility applications U.S.S.N. 09/375,333 [_____] and 09/374,958 [_____] (Attorney Docket Nos. STK-075 and STK-076) filed on even date herewith, also based on the aforementioned provisional application, the disclosures of which are herein incorporated by reference.

Page 8, first full paragraph:

Thus, in one aspect, the present invention is directed to a TGF-β superfamily chimeric protein derived from at least two different members of said superfamily, said chimeric protein comprising a dimer wherein one monomer comprises a finger 1 subdomain, a finger 2 subdomain and a heel subdomain, said finger 2 subdomain being derived from a first member of said superfamily, said finger 1 or heel subdomain being derived from a second, different member of said superfamily, wherein said monomer further comprises a conserved C-terminal cysteine skeleton. In a preferred embodiment, the finger 1 or heel subdomain is derived from the BMP-7, OP-1 (SEQ ID NO: 39). In other preferred embodiments, the finger 2 domain is derived from CDMP-2 (SEQ ID NO: 86) or BMP-2 (SEQ ID NO: 49). It is further contemplated that the chimeras of the instant invention can be homodimeric or heterodimeric.

Page 9, last paragraph:

Modified proteins of the invention can be used in conjunction with a biocompatible matrix such as, but not limited to, collagen, hydroxyapatite, ceramics or carboxymethylcellulose, or other suitable matrix material. Such combinations are particularly useful in methods for regenerating bone, cartilage and/or other non-mineralized skeletal or connective tissues such as but not limited to ligament, tendon, muscle, articular cartilage, fibrocartilage, joint capsule, menisci, intervertebral discs, synovial membrane tissue, and fasica to name but a few. See e.g. U.S. Patent No. 5,496,552, 5,674,292, 5,840,325 and U.S.S.N. 08/253,398, soon-to-issue as U.S. 5,906,827 [_____], the disclosures of which are incorporated by reference herein; also incorporated by reference herein are co-pending U.S.S.N. 08/459,129 and 08/458,811 each filed on June 2, 1995. The instant invention contemplates that the binding and/or adherence properties to such matrix materials can be altered using the domain swapping techniques disclosed herein.

Page 13, the brief description of figure 1:

Figure 1 lists the aligned C-terminal residues defining the finger 2 sub-domain for various known members of the BMP family, and TGF-β superfamily of proteins, starting with the first residue following the cysteine doublet. OP-1 (amino acid residues 66-102 of SEQ ID NO: 55); BMP-5 (amino acid residues 66-102 of SEQ ID NO: 52); BMP-6 (amino acid residues 66-102 of SEQ ID NO: 53); OP-2 (amino acid residues 66-102 of SEQ ID NO: 56); OP-3 (amino acid residues 66-102 of SEQ ID NO: 57); 60A (amino acid residues 82-118 of SEQ ID NO: 48); Vg-1 (amino acid residues 66-102 of SEQ ID NO: 46); Univin (amino acid residues 1-35 of SEQ ID NO: 34); BMP-2 (amino acid residues 66-102 of SEQ ID NO: 49); BMP-4 (amino acid residues 65-101 of SEQ ID NO:

51); GDF-5 (amino acid residues 66-102 of SEQ ID NO: 83); GDF-6 (amino acid residues 66-102 of SEQ ID NO: 85); GDF-7 (amino acid residues 66-102 of SEQ ID NO: 87); CDMP-2 (amino acid residues 66-102 of SEQ ID NO: 86); DPP (amino acid residues 66-102 of SEQ ID NO: 45); BMP-9 (amino acid residues 1-35 of SEQ ID NO: 7); Dorsalin (amino acid residues 66-103 of SEQ ID NO: 54); BMP-10 (amino acid residues 1-35 of SEQ ID NO: 8); GDF-3 (amino acid residues 65-101 of SEQ ID NO: 59); GDF-1 (amino acid residues 71-107 of SEQ ID NO: 58); SCREW (amino acid residues 1-35 of SEQ ID NO: 28); BMP-3 (amino acid residues 67-103 of SEQ ID NO: 50); NODAL (amino acid residues 1-34 of SEQ ID NO: 25); TGF-β1 (amino acid residues 63-98 of SEQ ID NO: 40); TGF-β2 (amino acid residues 63-98 of SEQ ID NO: 41); TGF-β3 (amino acid residues 63-98 of SEQ ID NO: 42); TGF-β4 (amino acid residues 63-98 of SEQ ID NO: 43); TGF-β5 (amino acid residues 63-98 of SEQ ID NO: 44); GDF-5 (amino acid residues 63-98 of SEQ ID NO: 40); Inhibin α (amino acid residues 66-105 of SEQ ID NO: 61); Inhibin βA (amino acid residues 70-106 of SEQ ID NO: 62); Inhibin βB (amino acid residues 70-106 of SEQ ID NO: 63); Inhibin βC (amino acid residues 1-35 of SEQ ID NO: 23); MIS (amino acid residues 1-34 of SEQ ID NO: 24); GDNF (amino acid residues 1-32 of SEQ ID NO: 19); BMP-11 (amino acid residues 1-35 of SEQ ID NO: 9); GDF-9 (amino acid residues 66-102 of SEQ ID NO: 60).

Page 13, the brief description of figure 3:

Figure 3 is a nucleotide sequence and the corresponding amino acid sequence of the OP-1 C-terminal seven cysteine active domain. The DNA sequence corresponds to nucleotides 1036-1341 of SEQ ID NO: 38. The protein sequence corresponds to amino acid residues 330-431 of SEQ ID NO: 39.

Pages 13-14, the brief description of figure 6:

Figures 6A, 6B, and 6C are sequence alignments using single letter amino acid code, arranged to indicate homologies of the finger 1, heel, and finger 2 regions, respectively, of some known members of the TGF-b superfamily. Shown are the respective amino acids comprising each region of human TGF-β1 through TGF-β5 (the TGF-β subgroup), the Vg/dpp subgroup consisting of dpp, Vg-1, Vgr-1, 60A (see copending U.S.S.N. 08/271,556), BMP-2A (also known in the literature as BMP-2), dorsalin, BMP-2B (also known in the literature as BMP-4), BMP-3, BMP-5, BMP-6, OP-1 (also known in the literature as BMP-7), OP-2 (see PCT/US91/07635 and U.S. Patent No. 5,266,683) and OP-3 (U.S.S.N 07/971,091), the GDF subgroup consisting of GDF-1, GDF-3, and GDF-9, the Inhibin subgroup consisting of Inhibin α, Inhibin βA, and Inhibin βB. The dashes (-) indicate a peptide bond between adjacent amino acids. A consensus sequence pattern for each subgroup is shown at the bottom of each subgroup. In Figure 6A the finger 1 sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 1-34 of SEQ ID NO:40); TGF-β2 (residues 1-34 of SEQ ID NO:41); TGF-β3 (residues 1-34 of SEQ ID NO:42); TGF-β4 (residues 1-34 of SEQ ID NO:43); TGF-β5 (residues 1-34 of SEQ ID NO:44); TGF-β pattern (1-34 of SEQ ID NO: 64); dpp (residues 1-34 of SEQ ID NO:45); Vg-1 (residues 1-34 of SEQ ID NO:46); Vgr-1 (residues 1-34 of SEQ ID NO:47); 60A (residues 1-34 of SEQ ID NO:48); BMP-2A (residues 1-34 of SEQ ID NO:49); DORSALIN (residues 1-34 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 1-34 of SEQ ID NO: 51); BMP-3 (residues 1-34 of SEQ ID NO: 50); BMP-5 (residues 1-34 of SEQ ID NO:52); BMP-6 (residues 1-34 of SEQ ID NO:53); OP-1/BMP-7 (residues 1-34 of SEQ ID NO:55); OP-2 (residues 1-34 of SEQ ID NO:56); OP-3 (residues 1-34 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 1-34 of SEQ ID NO:65); GDF-1 (residues 1-34 of SEQ ID NO:58); GDF-3 (residues 1-34 of SEQ ID NO:59); GDF-9 (residues 1-34 of SEQ ID NO:60); GDF subgroup pattern (residues 1-34 of SEQ

ID NO:66); Inhibin α (residues 1-34 of SEQ ID NO:61); Inhibin βA (residues 1-34 of SEQ ID NO:62); Inhibin βB (residues 1-34 of SEQ ID NO:63); Inhibin subgroup pattern (residues 1-34 of SEQ ID NO:67).

In Figure 6B the heel sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 35-64 of SEQ ID NO:40); TGF-β2 (residues 35-64 of SEQ ID NO:41); TGF-β3 (residues 35-64 of SEQ ID NO:42); TGF-β4 (residues 35-64 of SEQ ID NO:43); TGF-β5 (residues 35-64 of SEQ ID NO:44); TGF-β pattern (residues 35-64 of SEQ ID NO: 64); dpp (residues 35-67 of SEQ ID NO:45); Vg-1 (residues 35-67 of SEQ ID NO:46); Vgr-1 (residues 35-67 of SEQ ID NO:47); 60A (residues 35-67 of SEQ ID NO:48); BMP-2A (residues 35-66 of SEQ ID NO:49); DORSALIN (residues 35-67 of SEQ ID NO:54); BMP-2B/BMP-4 (residues 35-66 of SEQ ID NO: 51); BMP-3 (residues 35-68 of SEQ ID NO: 50); BMP-5 (residues 35-67 of SEQ ID NO:52); BMP-6 (residues 35-67 of SEQ ID NO:53); OP-1/BMP-7 (residues 35-67 of SEQ ID 35-67 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 35-68 of SEQ ID NO:65); GDF-1 (residues 35-72 of SEQ ID NO:58); GDF-3 (residues 35-66 of SEQ ID NO:59); GDF-9 (residues 35-67 of SEQ ID NO:60); GDF subgroup pattern (residues 35-72 of SEQ ID NO:66); Inhibin α (residues 35-67 of SEQ ID NO:61); Inhibin βA (residues 35-71 of SEQ ID NO:62); Inhibin βB (residues 35-71 of SEQ ID NO:63); Inhibin subgroup pattern (residues 35-71 of SEQ ID NO:67). In Figure 6C the finger 2 sequences correspond to the following SEQ ID NOS: TGF-β1 (residues 65-98 of SEQ ID NO:40); TGF-β2 (residues 65-98 of SEQ ID NO:41); TGF-β3 (residues 65-98 of SEQ ID NO:42); TGF-β4 (residues 65-98 of SEQ ID NO:43); TGF-β5 (residues 65-98 of SEQ ID NO:44); TGF-β pattern (residues 65-98 of SEQ ID NO: 64); dpp (residues 68-102 of SEQ ID NO:45); Vg-1 (residues 68-102 of SEQ ID NO:46); Vgr-1 (residues 68-102 of SEQ ID NO:47); 60A (residues 68-102 of SEQ ID NO:48); BMP-2A (residues 68-102 of SEQ ID NO:49); DORSALIN (residues 68-103 of SEQ ID NO:54); BMP-2B/BMP-4

(residues 68-102 of SEQ ID NO: 51); BMP-3 (residues 68-102 of SEQ ID NO: 50); BMP-5 (residues 68-102 of SEQ ID NO:52); BMP-6 (residues 68-102 of SEQ ID NO:53); OP-1/BMP-7 (residues 68-102 of SEQ ID NO:55); OP-2 (residues 68-102 of SEQ ID NO:56); OP-3 (residues 68-102 of SEQ ID NO:57); Vg/dpp subgroup pattern (residues 68-103 of SEQ ID NO:65); GDF-1 (residues 73-107 of SEQ ID NO:58); GDF-3 (residues 67-101 of SEQ ID NO:59); GDF-9 (residues 68-102 of SEQ ID NO:60); GDF subgroup pattern (residues 73-107 of SEQ ID NO:66); Inhibin α (residues 68-105 of SEQ ID NO:61); Inhibin βA (residues 72-106 of SEQ ID NO:62); Inhibin βB (residues 72-106 of SEQ ID NO:63); Inhibin subgroup pattern (residues 72-109 of SEQ ID NO:67).

Page 14, the brief description of figure 7:

Figure 7 is a single letter code listing of amino acid sequences, identified in capital letter in standard single letter amino acid code, and in lower case letters to identify groups of amino acids useful in that location, wherein the lower case letters stand for the amino acids indicated in accordance with the pattern definition key table set forth in Figure 8. Figure 7 identifies preferred pattern sequences for constituting the finger 1, heel, and finger 2 regions of biosynthetic constructs of the invention. The dashes (-) indicate a peptide bond between adjacent amino acids. The SEQ ID NOS for the subgroup patterns are as follows: TGF-β subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:64); TGF-β subgroup pattern heel (residues 35-64 of SEQ ID NO:64); TGF-β subgroup pattern finger 2 (residues 65-98 of SEQ ID NO:64); Vg/dpp subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:65); Vg/dpp subgroup pattern heel (residues 35-68 of SEQ ID NO:65); Vg/dpp subgroup pattern finger 2 (residues 69-104 of SEQ ID NO:65); GDF subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:66); GFD subgroup pattern heel (residues 35-72 of SEQ

ID NO:66); GDF subgroup pattern finger 2 (residues 73-107 of SEQ ID NO:66); Inhibin subgroup pattern finger 1 (residues 1-34 of SEQ ID NO:67); Inhibin subgroup pattern heel (residues 35-71 of SEQ ID NO:67); Inhibin subgroup pattern finger 2 (residues 72-109 of SEQ ID NO:67).

Page 19, second full paragraph:
As used herein, the "base" or "neck" region of the finger 2 sub-domain is defined by residues 1-10 and 22-31, as exemplified by OP-1 (residues 67-77 and 89 to 98 of SEQ ID NO:55), and counting from the first residue following the cysteine doublet in the C-terminal active domain. (See Fig. 1). As is readily apparent from a sequence alignment of other TGF-β superfamily protein members with OP-1, the corresponding base or neck region for a longer protein, such as BMP-9 or Dorsalin, is defined by residues 1-10 and 23-32 (residues 67-77 and 90-99 of SEQ ID NO:54); for a shorter protein, such as NODAL, the corresponding region is defined by residues 1-10 and 22-30 (amino acid residues 1-10 and 22-30 or SEQ ID NO: 25) (See Fig. 1). In SEQ ID NO: 39, (human OP-1), the residues corresponding to the base or neck region of the finger 2 subdomain are residues 397-406 (corresponding to residues 1-10 in Fig. 1) and residues 418-427 (corresponding to residues 22-31 in Fig. 1).

Page 31, first full paragraph:
Amino acid sequence patterns showing amino acids preferred at each location in the finger and heel regions, deduced in accordance with the principles described in Smith et al. (1990) supra, also are show in Figs. 6-7, and are referred to as the: TGF-β (SEQ ID NO: 64); Vg/dpp (SEQ ID NO: 65); GDF (SEQ ID NO: 66); and Inhibin (SEQ ID NO: 67) subgroup patterns. The amino acid sequences defining the finger 1, heel and finger 2 sequence patterns of each

subgroup are set forth in Figs. 6A, 6B, and 6C, respectively. In addition, the amino acid sequences defining the entire TGF-b, Vg/dpp, GDF and Inhibin subgroup patterns are set forth in the Sequence Listing as SEQ. ID. Nos. 64, 65, 66, and 67, respectively.